HAM-TMC LIBRARY INTERLIBRARY LENDING ARTICLE/PHOTOCOPY

Wednesday, September 08, 2004

ILLiad TN: 92463
ILL Number: 8293443

Shipping Address:
Oregon State Library
Interlibrary Loan
Salem, OR 97310-0640

Borrower: OSO System: OCLC

Maxcost: 20.00 ifm

Lending String: AZS,*TMC,ITB,CUY,CUY

Patron: Zlot, Amy

Journal Title: Diabetes, obesity & metabolism.

Volume: 6 **Issue:** 3
Month/Year: 05 2004**Pages:** 187-94

Article Author:

Article Title: Molyneaux, L; Strong family history predicts a younger age of onset
for subjects diagnosed with type 2 diabetes.

(S) Batch: (S) Invoice #:

Solomon-ID:
Billing Category: OUTREGION
EFTS: No

Document Charges:	$11.00
Additional Charges:	
Total Due:	

Call #/Location:

Reasons-for-Non-Supply

___ BDY (At Bindery)
___ CST (Cost exceeds stated maxcost)
___ INC (Not as Cited)
___ LAC (Lacking volume/issue)
___ LOS (Lost)
___ NYR (Not Yet Received)
___ NOS (Not on Shelf)
___ NOT (Title Not Owned)
___ OTH (Other) Specify:___

DELIVERY: Ariel

Fax: 503-588-7119
Ariel: 159.121.122.36
Phone: 503-378-4277 x2

This document has been supplied to you from:

OCLC: **TMC**
DOCLINE: **TXUTEX**

44-HOU via TExpress
HAM-TMC Library
1133 JOHN FREEMAN BLVD
HOUSTON, TX 77030

Hours: Monday - Friday, 8am - 5pm
Phone: 713-799-7159
Fax: 713-790-7056
ARIEL: 192.68.30.164
Email: TMCARIEL@LIBRARY.TMC.EDU

Thank You for Using Our Services!

THIS IS NOT AN INVOICE!
PLEASE WAIT TO BE BILLED.

ORIGINAL ARTICLE

Strong family history predicts a younger age of onset for subjects diagnosed with type 2 diabetes

L. Molyneaux,[1] M. Constantino[1] and D. Yue[1,2]

[1]The Diabetes Centre, Royal Prince Alfred Hospital, Sydney, NSW, Australia
[2]The Department of Medicine, The University of Sydney, Sydney, NSW, Australia

Aims: Age of onset of type 2 diabetes is becoming earlier and with it there is an increase in the development of chronic complications. This study examined the relationship between the strength of family history of diabetes on (i) age of diabetes onset and (ii) prevalence of diabetic complications.
Research design and methods: Data on family history of diabetes and age of diabetes onset were prospectively collected on 5193 subjects. Family members were deemed to include grandparents, parents, siblings, aunts/uncles and children. To adjust for family size and to assess effects of pathway to diagnosis, we also contacted a subset of 180 patients selected on the basis of the strength of family histories of diabetes. A full assessment for diabetic complications including retinopathy, neuropathy and renal and macrovascular status was performed for the total cohort.
Results: The more cases of diabetes found in a family, the younger the age of onset of type 2 diabetes. This phenomenon does not appear to be due to patients with strong family history of diabetes being more concerned about the possibility of having diabetes. The effect of strong family history is also evident in many ethnic groups when examined individually, although they differ from each other in their characteristic age of onset of diabetes. Once adjusted for duration of diabetes, strength of family history does not appear to affect metabolic profiles or prevalence of chronic complications.
Conclusions: There is a strong relationship between the number of affected family members with diabetes and age of developing diabetes. The genetic and environmental factors underlying this phenomenon remain to be elucidated. However, it may be one of the reasons explaining why type 2 diabetes is affecting younger people worldwide.
Keywords: age of diabetes onset, complications, family history of diabetes, type 2 diabetes
Received 16 July 2003; returned for revision 5 November 2003; revised version accepted 7 November 2003

Introduction

Diabetes is a major chronic disease with profound implications for both individual health and also medicoeconomic cost of every nation. Moreover, the prevalence of diabetes is increasing worldwide. It is conservatively estimated that currently about 7% of the population has diabetes and by year 2025 three hundred millions of people would be affected by this disorder [1].

The pathogenesis of type 2 diabetes is complex, incompletely understood and likely to involve an intricate interplay between genetic and environmental factors. There is also an interesting but serious observation that the age of onset of type 2 diabetes is becoming younger [2,3]. This is of great importance because with a younger age of onset, the patient has a longer life expectancy and therefore increased propensity to

Correspondence:
Ms Lynda Molyneaux, Diabetes Centre, Royal Prince Alfred Hospital, Camperdown, NSW, Australia 2050.
E-mail:
lynda@email.cs.nsw.gov.au

develop the various chronic complications of diabetes. This is then ultimately translated into a much higher cost of treating diabetes. Previous studies have examined the familial pattern of type 2 diabetes and how this might affect clinical characteristics of diabetes [4–6]. In this study, we examined in detail the family history of diabetes and determined how it might affect age of onset and other clinical parameters of diabetes. The extensive computer records collected prospectively on all our patients, together with the multicultural nature of our society, allowed a large cohort of patients from different ethnic groups to be studied in this regard.

Materials and Methods

Patients attending the Diabetes Centre of Royal Prince Alfred Hospital are referred by their primary care physicians, and predominantly live within the Sydney Metropolitan area. The patients come from a broad range of ethnic backgrounds with only 37% of patients having Anglo-Celtic origin. To examine the effect of the strength of family history on the age of diabetes onset, age at diagnosis and family history were collected on all patients attending the Centre for a complication assessment over a 10-year period. Patients were determined as having type 1 or type 2 diabetes according to WHO criteria [7] and only patients with type 2 diabetes were included in the study. A total of 5193 met this criterion. In the study of this total cohort, family members were deemed to include grandparents, parents, siblings, aunt/uncles and children. In the study of a smaller cohort to adjust for family size (see below), only parents and siblings were considered as family members.

Diabetes Status and Complications

All patients underwent assessment for diabetes complication status and metabolic control. Blood pressure was measured in duplicate after patient had been in a sitting position for at least 10 min, and the mean result reported. Fundi were examined by direct ophthalmoscopy by a single observer. Albuminuria was quantified by measurement of albumin concentration in spot urine sample using a commercially available radioimmunoassay kit by diagnostic product (UK), and nephropathy was considered to be present when there was microalbuminuria (> 30 mg/l) or overt proteinuria (> 0.5 g/l). Neuropathy was defined as a vibration perception threshold of > 30 V tested with a biothesiometer (OH, USA). The presence of macrovascular disease including ischaemic heart disease, cerebrovascular disease and peripheral vascular disease was noted. HbA1c was measured using high-performance liquid chromatography (BIO-RAD, CA, USA; CV < 2%). Plasma total cholesterol and fasting triglycerides were measured by enzymatic techniques on a Roche 917 auto analyser. High-density lipoprotein cholesterol (HDLc) was determined on the same instrument using a cyclodextim-based homogeneous assay. All physician examination and laboratory results were recorded in our in-house purpose-designed computer data system [8].

The Effects of Family Size and Pathway to Diagnosis

To adjust for the effects of family size and to assess the effects of pathway to diagnosis of diabetes, a short questionnaire was developed and sent to a subset of 180 patients. They were selected only on the basis of the strength of their family history of diabetes (i.e. diabetes in 0, 1 or > 5 members of family). In the questionnaire, patients were asked:

1. When you first had diabetes, did you go to your doctor because you had symptoms of diabetes (such as thirst, tiredness, passing a lot of urine)?
2. Was your diabetes diagnosed on a routine check up when you were feeling fine?
3. How many brothers and sisters do you have? From this the percentage of family (2 parents plus siblings) with diabetes can be calculated.

Statistical Analysis

Statistical analysis was performed using the NCSS97 statistical software package (Dr Jerry Hintze, Kaysville, UT, USA). Subjects were grouped according to the number of family members that were affected by diabetes, ranging from nil to > 6 relatives affected. Data were assessed for normality and if necessary normalized using log transformation. Continuous data were expressed as median and interquartile range (IQR). ANOVA was used for comparison of continuous variables grouped by the number of family members affected by diabetes and ethnicity. Effect modification was assessed for age of diagnosis between the number of family members affected and ethnicity. Analysis of covariance was used to adjust for any known confounders. A test for trend was performed for age of diagnosis and the number and percentage of family members that were affected by diabetes. When multiple comparisons were performed, adjustment was made using the Bonferroni method at $p < 0.01$. To control for family size, the total number of siblings and parents with diabetes was expressed as a percentage of total number of family members in this category. Multiple regression was used to assess the relationship between age of diagnosis and the percentage of families affected with diabetes. Categorical data were analysed by the χ^2 test and are reported as a percentage and 95% confidence intervals (95% CI). Logistic regression was used to assess for differences in prevalence of diabetes-specific complications between each family history strata, grouped by quartiles of duration of diabetes. Statistical significance was accepted at a p value of < 0.05.

Results

Family History

A total of 2939 (56.6%; 95% CI: 55.2–57.9%) of the type 2 diabetic subjects studied had a family history of diabetes. Maternal diabetes was twice as common than paternal diabetes (19.7%; 95% CI 18.6–20.8% vs. 10.2%; 95% CI 9.4–11.1%).

There was a very strong inverse relationship between the strength of family history and age of onset of diabetes ($t_{trend} = 243.1$; $p < 0.0001$) (fig. 1). Such a relationship remained demonstrable ($t_{trend} = 59.3$; $p < 0.0001$) when the strength of family history of diabetes in the 180 families surveyed was expressed as percentage of family affected and grouped into tertiles (fig. 2) or when the family size was analysed as a covariate ($F_{2df} = 16.4$; $p < 0.0001$). When analysed as continuous variables, the age of diagnosis of diabetes reduces by 1.7 years for every 10% increase in family members affected by diabetes ($r = 0.23$, $p = 0.006$). As seen in fig. 3, the relationship between strength of family history and age of onset of diabetes remained significantly different even when grouped by ethnicity ($F_{6df} = 6.3$; $p < 0.0001$). Despite patients of Indian, Australian Aboriginal and Pacific Islander descent being diagnosed at an earlier age than their counterparts regardless of family history ($F_{6df} = 23.9$; $p < 0.0001$), there was no evidence of effect modification by ethnicity ($F_{36df} = 0.6$; $p = 1.0$). There was however, an over-representation of persons from non-English-speaking backgrounds in the group of patients with > 5 relatives affected by diabetes, particularly Australian Aborigines and Pacific Islanders. There was also significant effect modification found for gender and strength of family history, with the proportion of females affected increasing as the strength of family history increased ($F_{6df} = 2.6$; $p = 0.02$).

Diabetes Status and Complications

As seen in table 1, patients with a family history tended to have a longer duration at time of initial assessment. Despite this, there were no statistical differences in modes of diabetes treatment between groups. Moreover, strength of family history did not effect glycaemic control or lipid levels (table 2). Patients with strong family history had lower blood pressure and an increased prevalence of blood pressure treatment; however, when adjusted for age this result was not significant.

As seen in fig. 4, the strength of family history of diabetes did not have significant effects on prevalence of retinopathy once duration of diabetes was stratified. The same conclusion is true for neuropathy, nephropathy and macrovascular disease (results not shown).

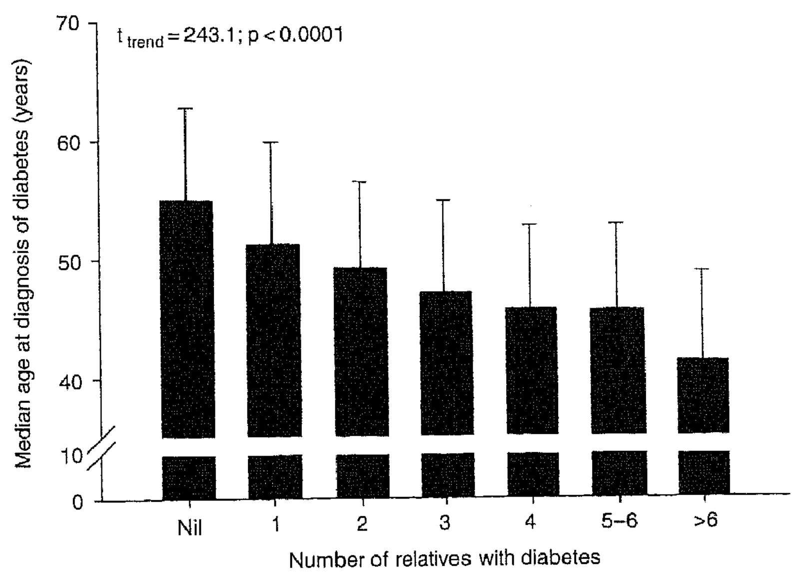

Fig. 1 The relationship between strength of family history of diabetes and age of onset of diabetes. Family history is expressed as absolute number of subjects in the family with diabetes.

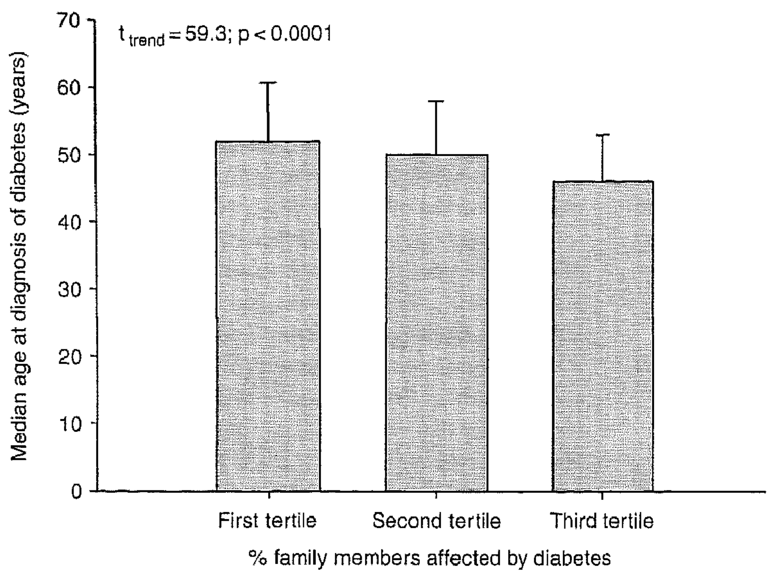

Fig. 2 The relationship between strength of family history of diabetes and age of onset of diabetes. Family history is expressed as percentage of family members with diabetes, grouped into tertiles.

Diagnosis Pathway

Diagnosis pathway was examined for the subset of 180 patients selected to receive the short questionnaire. A total of 135 (75%) completed questionnaires were returned. As seen in table 3, there was no difference in the presence of symptoms at the time of diagnosis between patients with or without a family history of diabetes. Similar proportions of patients in each group were diagnosed with diabetes during routine checkup. However, patients with a strong family history had significantly more siblings than those without a family history ($\chi^2_{2df} = 38.0$; $p < 0.0001$).

Discussion

Our study showed that the strength of family history is critically related to a very important phenotypic characteristic of type 2 diabetes, its age of onset [10,11]. When Ng *et al.* [9] arbitrarily divided their Chinese patients into those <35 years and >35 years at onset of diabetes, they found that paternal history of diabetes was a predictor of early onset in males whilst both paternal and maternal diabetes predicted younger age of onset in females. These findings were broadly in agreement with those of Bo *et al.* [4] who found in a group of Italian patients that the presence of parental diabetes was also

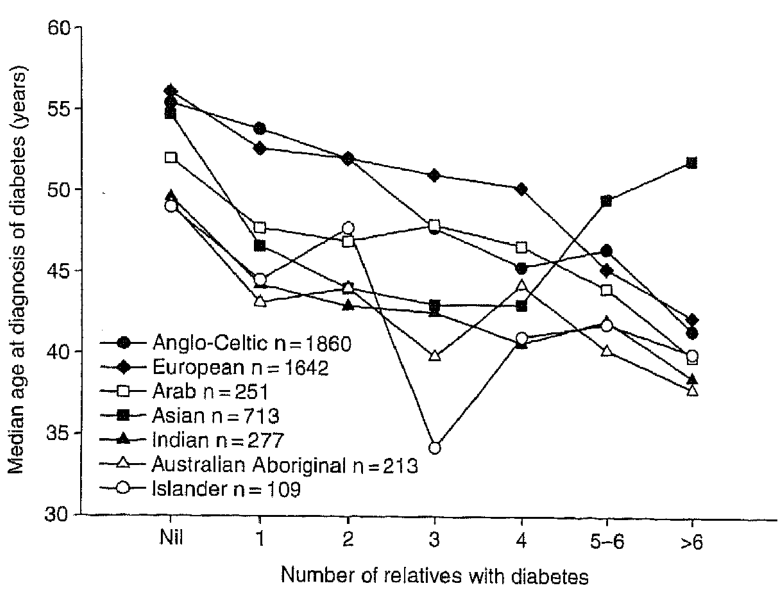

Fig. 3 The relationship between strength of family history of diabetes and age of onset of diabetes amongst various ethnic groups.

Table 1 Demographic profile for patients with type 2 diabetes grouped by strength of family history at initial visit

	Nil (n = 2256)	1 (n = 1634)	2 (n = 747)	3 (n = 296)	4 (n = 128)	5–6 (n = 86)	>6 (n = 46)	Test statistics; p value
Age at initial visit (years)	61.1 (53.4–68.3)	58.0* (48.9–66.3)	55.7* (47.4–63.7)	53.9* (45.3–63.4)	52.9* (44.8–63.4)	53.3* (47.9–61.4)	50.0* (43.5–57.5)	$F_{6df} = 41.5$; $p < 0.0001$
Duration of diabetes (years)	2.9 (0.3–8.3)	3.5 (0.4–9.6)	3.6 (0.4–9.7)	4.1 (0.5–11.1)	5.5 (0.4–12.2)	5.4* (0.8–12.2)	5.9 (1.6–10.7)	$F_{6df} = 4.4$; $p = 0.0002$
Male (%)	60.5	55.7	50.2	48.0	44.5	41.9	45.7	$\chi^2_{6df} = 52.8$; $p < 0.0001$
Anglo-Celtic (%)	35.6	35.8	39.7	36.1	36.7	20.9	13.0	$\chi^2_{6df} = 23.6$; $p = 0.0006$
Diabetic Rx at initial visit (%)								$\chi^2_{6df} = 8.7$; $p = 0.7$
Diet	26.7	26.0	26.6	26.8	24.8	25.6	23.8	
Tablets	63.3	62.4	62.0	59.3	59.5	61.5	66.7	
Insulin	10.0	11.6	11.5	13.9	15.7	12.8	9.5	

*Bonferroni adjustment, different to nil; $p < 0.05$

Table 2 Clinical profile for patients with type 2 diabetes grouped by strength of family history at the initial visit

	Nil	1	2	3	4	5–6	>6	Test statistics; p value
HbA1c (%)	7.7 (6.5–9.2)	7.8 (6.7–9.5)	8.0 (6.8–9.5)	8.1 (6.6–9.6)	7.7 (6.8–9.2)	7.7 (6.9–9.6)	8.3 (6.9–9.3)	$F_{6df} = 1.6$; $p = 0.2$
Cholesterol (mmol/L)	5.4 (4.7–6.2)	5.5 (4.8–6.3)	5.5 (4.8–6.3)	5.5 (4.9–6.3)	5.4 (4.8–6.2)	5.5 (4.9–6.0)	5.4 (4.6–5.9)	$F_{6df} = 0.7$; $p = 0.7$
HDLc (mmol/L)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (1–1.4)	1.1 (0.9–1.3)	1.1 (1–1.4)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	$F_{6df} = 1.5$; $p = 0.2$
Triglycerides (mmol/L)	2 (1.4–3)	2.1 (1.4–3.2)	2 (1.4–3.1)	2 (1.4–3.1)	2 (1.5–2.9)	1.9 (1.3–2.7)	1.7 (1.4–2.7)	$F_{6df} = 0\ 4$; $p = 0.9$
Systolic BP (mmHg)	136 (124–150)	134 (121–149)	130 (120–145)	130 (120–144)	130 (120–144)	130 (117–140)	130 (117–141)	$F_{6df} = 1.3$;$p = 0.3$ (adjusted for age)
Diastolic BP (mmHg)	80 (72–90)	80 (72–90)	80 (75–88)	80 (75–89)	80 (70–86)	79 (70–80)	80 (72–82)	$F_{6df} = 1.5$; $p = 0.2$
BP Rx (%)	46.5	42.5	40.0	38.0	34.7	40.4	34.5	$\chi^2_{6df} = 2.2$; $p = 0.8$ (adjusted for age)
BMI (kg/m^2)	29.0 (25.8–33.1)	29.4 (26.0–33.2)	29.6 (26.1–33.5)	30.2 (26.9–34.8)	29.5 (26.4–34.7)	30.7 (26.0–33.6)	29.4 (25.9–34.5)	$F_{6df} = 1.7$; $p = 0.1$

HDLc, high-density lipoprotein cholesterol; BMI, body mass index.

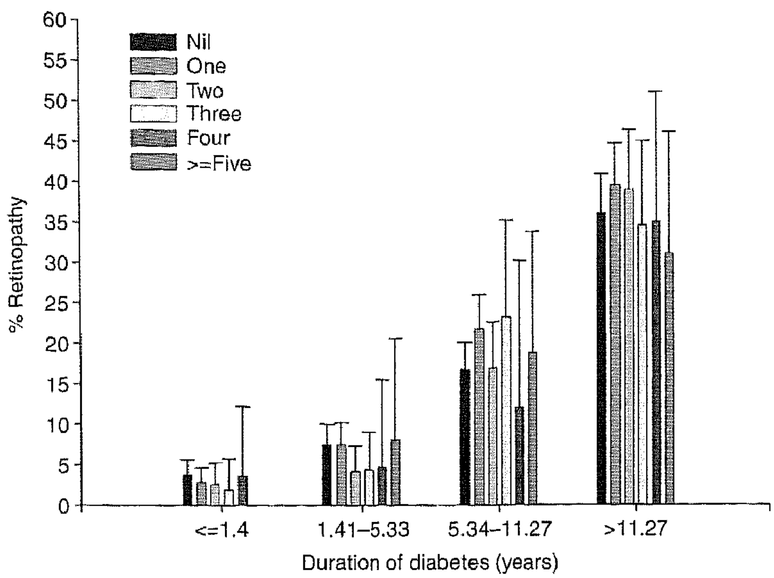

Fig. 4 The relationship between strength of family history and the prevalence of retinopathy. Patients were stratified according to their duration of diabetes.

associated with younger age of onset of diabetes in the offspring. The San Antonio Family Diabetes Study found that relatives of patients with diabetes onset at age < 40 years are at more risk of developing diabetes [12]. Our study took a different approach from these previous studies in that the number of family members with diabetes was treated as the independent variable. This allowed the age of onset of diabetes in our cohort to be treated as a continuous variable, avoiding the need of dividing the patients into groups according to some arbitrarily defined age threshold. This approach had enabled us to show that the age of onset of diabetes continued to fall when more and more family members, beyond the parents, were affected by diabetes. Information for this study was collected prospectively over a period of 10 years from a database, which ran to several pages in length. In a study of this nature, it is always a compromise what parameters can be collected. We did not record the size of the family and therefore could not adjust our results according to family size in the total cohort. However, the smaller cohort that was contacted also showed an inverse relationship between strength of family history and age of onset of diabetes, consistent with our conclusion. Our findings applied equally to the several common ethnic groups in our community and therefore likely to be applicable to many other populations residing in other parts of the world. It is noteworthy that in our cohort, the prevalence of diabetic complications and degree of glyceamic control were not affected by the strength of family history, once adjusted for the duration of diabetes. It is pertinent to emphasize that in the real-life situation without such statistical adjustment, patients with early onset would likely be exposed to hyperglycaemia for longer and are more prone to diabetic complications. They therefore require aggressive treatment as early as possible.

At this stage of our understanding, explanation of the phenomenon we have observed is not entirely apparent. Although relying on patient memory to determine family history is obviously subjected to recall bias, the San Luis

Table 3 Questionnaire results

	Presence of symptoms of diabetes (%)	Diabetes diagnosed at routine checkup (%)	Number of siblings*
Nil family history (n = 39)	42†	62‡	2 (1–3)§
1 family member (n = 41)	40	60	3 (1–5)
≥5 family members (n = 55)	48	67	6 (3–8)

*Median and interquartile range.
†$\chi^2_{2df} = 0.7$; $p = 0.7$.
‡$\chi^2_{2df} = 0.5$; $p = 0.8$.
§$\chi^2_{2df} = 38.4$; $p < 0.0001$.

Valley Diabetes Study [13] showed that by and large, patients reported family history of diabetes accurately. The strength and the consistency of the association between number of relatives affected with diabetes and age of onset also argued against faulty recall as the sole explanation for our results. Our questionnaire survey suggests that increased patient awareness of diabetes and therefore the need for early screening also did not appear to play a major role.

In a small minority of patients with diabetes, the inheritance pattern is well defined. For example, in patient's with maturity-onset diabetes of the young (MODY) or diabetes due to mutations of the insulin receptor, a clear autosomal pattern can be observed. In the great majority of patients, however, the genetic factors controlling the development of type 2 diabetes is incompletely understood and the common form of this disease is currently considered to be polygenic in aetiology [14–17]. It is possible that one or more combination of these diabetogenic genes is characterized by both high penetrance (and therefore affecting many family members) and early defects in insulin secretion or action (and therefore a younger age of onset). Alternatively, the total number of diabetogenic genes inherited may be characteristic of each family and a high number would make that family manifest more diabetes and at an earlier age. The concept that greater genetic load is associated with younger age of onset is supported by the observation of a 'double gene dose' resulting in younger age of onset in those with bi-parental type 2 diabetes [18]. Environmental factors are also known to play powerful roles in the pathogenesis of type 2 diabetes. Numerous studies have confirmed the importance of obesity, in-utero nutritional and sedentary life style in this regard. In addition to large family size, our data also showed a relationship between early age of diabetes onset with the female gender. Sellers *et al.* [19] conducted a study showing an earlier onset of diabetes in patients with HNF-1[alpha] G319S mutation. There are likely to be many other risk factors yet to be discovered. One or more of these environmental and genetic factors shared by a family could make its members exhibiting diabetes more frequently and earlier.

It is likely that a complex interaction of genetic and environmental factors determines not only the development but also the phenotypic profile of type 2 diabetes. Further understanding of the mechanism underlying the relationship we have observed between age of onset and strength of family history is of great importance. It may help to explain the widely observed, but poorly understood, phenomenon that all over the world, type 2 diabetes is affecting patients of younger and younger age groups [20]. In fact it is estimated that the world now has more young type 2 than young type 1 diabetic patients. Apart from impairing the quality of their lives at an early age, these patients with early onset diabetes are particularly prone to chronic complications of this disease because they will be exposed to the abnormal metabolic milieu of diabetes for a longer time. This is one of the reasons why the world is witnessing an explosion of end stage renal disease in people with type 2 diabetes with grave personal and economic consequences.

References

1 King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; **21:** 1414–1431.

2 Mokdad A, Ford E, Bowman B *et al.* Diabetes trends in the US 1990–98. Diabetes Care 2000; **23:** 1278–1283.

3 Riste L, Khan F, Cruickshank K. High prevalence of type 2 diabetes in all ethnic groups, including Europeans, in a British inner city. Diabetes Care 2001; **24:** 1377–1383.

4 Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Influence of a familial history of diabetes on the clinical characteristics of patients with type 2 diabetes mellitus. Diabet Med 2000; **17:** 538–542.

5 Lee SC, Ko GTC, Lt JKY *et al.* Factors predicting the age when type 2 diabetes is diagnosed in Hong Kong Chinese subjects. Diabetes Care 2001; **24:** 646–649.

6 Mitchell BD, Kammerer CM, Reinhart LJ, Stern MP. NIDDM in Mexican-American families: Heterogeneity by age of onset. Diabetes Care 1994; **17:** 567–573.

7 World Health Organization. Diabetes Mellitus: Report of a WHO Study Group. Geneva: World Health Organization, 1985 (Technical Report Ser., no. 727).

8 Mcgill M, Molyneaux LM, Yue DK, Turtle JR. A single visit diabetes complication assessment service: a complement to diabetic management at the primary care level. Diabet Med 1993; **10:** 366–370.

9 Ng MCY, Lee SC, Ko GTC *et al.* Familial early-onset type 2 diabetes in Chinese patients: Obesity and genetics have more significant roles than autoimmunity. Diabetes Care 2001; **24:** 663–671.

10 Owen K, Ayres S, Corbett S, Hattersley A. Increased risk of diabetes in first-degree relatives of young-onset type 2 diabetic patients compared with relatives of those diagnosed later. Diabetes Care 2002; **25:** 636–637.

11 Lev-Ran A, Sprecher E, Yerushalmy Y, Schindel B, Kisch ES. Homogeneity of the age at diagnosis in sibs with type 2 diabetes: implications for sib-pair analysis. Am J Med Genet 2000; **91:** 91–95.

12 Mitchell BD, Valdez R, Hazuda HP, Haffner SM, Monterrosa A, Stern MP. Differences in the prevalence of diabetes and impaired glucose tolerance according to maternal or paternal history of diabetes. Diabetes Care 1993; **16:** 1262–1266.

13 Kahn LB, Marshall, Baxter J, Shetterly SM, Hamman RF. Accuracy of reported family history of diabetes mellitus: Results from San Luis Valley Diabetes Study. Diabetes Care 1990; **13:** 796–798.

14 Poulsen P, Kyvik KO, Vaag A, Beck-Nielsen H. Heritability of type 11 (non-insulin dependent) diabetes mellitus and abnormal glucose tolerance: a population-based twin study. Diabetologia 1999; **42:** 139–145.

15 Rimoin DL. Genetics of diabetes mellitus. Diabetes 1967; **16:** 346–351.

16 Barnett AH, Eff C, Leslie RDG, Pyke DA. Diabetes in identical twins. Diabetologia 1981; **20:** 87–93.

17 Frayling TM, Walker M, McCarthy MI *et al.* Parent-offspring trios: a resource to facilitate the identification of type 2 diabetes genes. Diabetes 1999; **48:** 2475–2479.

18 O'Rahilly S, Spivey RS, Holman RR *et al.* Type II diabetes of early onset: a distinct clinical and genetic syndrome? BMJ 1987; **294:** 923–928.

19 Sellers EAC, Triggs-Raine B, Rockman-Greenberg C, Dean HJ. The prevalence of the HNF-1[alpha]G319S mutation in Canadian aboriginal youth with type 2 diabetes. Diabetes Care 2002; **25:** 2202–2206.

20 Rosenbloom AL, Joe JR, Young RS, Winter WE. Emerging epidemic of type 2 diabetes in youth. Diabetes Care 1999; **22:** 345–354.